Cyclosporin treatment of perianal fistulas in dogs

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Abstract — The purpose of this pilot study was to investigate the efficacy of cyclosporin in treating perianal fistulas (PAF) in dogs. Based on resolution of all fistulas in all dogs with remission times up to >18 months, we conclude that cyclosporin therapy is the treatment of choice for PAF in dogs.

Résumé — Utilisation de la cyclosporine dans le traitement des fistules périanales chez le chien. L'objectif de cette étude préliminaire consistait à étudier l'efficacité de la cyclosporine dans le traitement des fistules périanales (FPA) chez le chien. Considérant qu'il y a eu résolution de toutes les fistules chez tous les chiens et que les temps de rémission allaient jusqu'à plus de 18 mois, nous avons conclu qu'une thérapie à la cyclosporine était le traitement de choix lors de FPA chez le chien.

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Perianal fistula (PAF) is a well-documented, painful, chronic, progressive inflammatory disease involving the anal and perianal area of dogs (1–4). Medical management has proved to be unsuccessful in achieving resolution of lesions (4,5), and current treatment options are of various surgical techniques (4–7). A recent review of current surgical methods for PAF indicates good to poor outcome and low to high recurrence rates (1). All the methods are invasive, frequently requiring multiple treatments and postoperative management by the owner. Similarities in the clinical appearance of canine PAF and PAF in humans with Crohn's disease have been reported (2). In both instances, the etiology is yet unknown. However, in Crohn's disease, the immune system is thought to play an important role (8). In dogs, an abnormality in immune function has been suggested; however, no mechanism has been elucidated (9). A recent study demonstrating the efficacy of cyclosporin in the treatment of anal fistulas in human patients with Crohn's disease (10) was the impetus for cyclosporin treatment in dogs with PAF in this report.

Eight German shepherds (GSD) and 1 Border collie were examined at the Veterinary Teaching Hospital (VTH) of the Ontario Veterinary College and 1 GSD was examined at the Saint John Animal Hospital, Saint John, New Brunswick, between July 1994 and August 1995 for assessment of PAF. Seven of the dogs had received surgical treatment for this disease previously, and the owners felt strongly about not subjecting their dogs to this method of treatment again. In 3 dogs, this was the first occurrence of PAF and the owner declined surgical treatment. Physical examination confirmed the presence of PAF. There was no evidence of anal sac involvement in any of the dogs in which prior anal sacculectomy had not been performed. Otherwise, all dogs were healthy.

Since surgical treatment was not an option, especially for those owners with previous experience in postsurgical management, cyclosporin treatment was discussed with the owners, all of whom were willing to try this therapeutic approach. Cyclosporin (Sandimmun, Sandoz Canada, Dorval, Quebec) was commenced at 10 mg/kg body weight (BW), PO, q12h, in dogs 1,2, and 4. After 1 wk, this dose was reduced to between 5.0 and 7.5 mg/kg BW, q12h, due to the high trough cyclosporin blood measurements at 10 mg/kg BW. In the remaining dogs, cyclosporin treatment was commenced at 7.5 mg/kg BW, q12h. After 1 wk of therapy, the dogs were presented to the VTH, or the referring veterinarian, for examination and blood collection for a 12-hour, whole blood cyclosporin trough measurement. The dose of cyclosporin was adjusted to attain whole blood cyclosporin trough measurements of 400–600 ng/mL, as measured by monoclonal radioimmunoassay (Inkstar, Stillwater, Minniapolis, Minnesota, USA). Where antibiotics were prescribed, trimethoprim sulphamethoxazole (TMS) (Novo-Trimel, Novopharm, Scarborough, Ontario), 15 mg/kg BW, PO, q12h, or cephalexin (Novo-Lexin, Novopharm), 25 mg/kg BW, PO, q8h, was administered. Where analgesia/sedation was required for examination, oxymorphone (Numorphan, Dupont Pharma, Mississauga,

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Table 1. Demographic and clinical data of each dog with perianal fistula (PAF) receiving cyclosporin therapy

Case No.	Signalment	Duration of PAF prior to therapy	Previous treatment	Extent of PAF involvement	Duration of therapy	Remission after cessation of therapy
1	10-year-old, intact, male GSD	2 mo	None	0°–360°, up to 5 cm deep	12 wk	>18 mo
2	8-year-old, intact, male GSD	10 mo	3 surgical resections, antibiotics, and daily cleansing	90°–180°, up to 2.5 cm deep	8 wk initially. Recurrence requiring a 2nd, 8-wk trial	10 mo after 2nd trial
3	4-year-old, castrated, male GSD	3 mo	1 surgical resection	0°–180°, superficial	8 wk initially. Recurrence requiring a 2nd, 4-wk trial	Surgery 7 mo after 2nd period of therapy. Remission >6 mo
4	7-year-old, intact, female GSD	8 mo	1 surgical resection, antibiotics, daily cleansing	0°–90°, up to 0.5 cm deep	16 wk	>12 mo
5	4-year-old, intact, male GSD	6 mo	Several antibiotics, daily cleansing	0°–360°, up to 10 cm deep	20 wk	>8 mo
6	3-year-old, spayed, female GSD	15 mo	Rectal pull-through, tail amputation, debridement, several antibiotics, daily cleansing	0°–180°, 2.5 cm deep	12 wk	>8.5 mo
7	5-year-old, castrated, male GSD	7 mo	2 surgical resections, daily cleansing	0°–360°, depth not noted	16 wk	>8 mo
8	9-year-old, castrated, male GSD	3 mo	1 surgical resection,daily cleansing	0°–360°, up to 4 cm deep	8 wk	>11 mo
9	3.5-year-old, castrated, male GSD	5 mo	Antibiotics	0°–270°, superficial	8 wk initially. Recurrence requiring a 2nd, 8-wk therapy	8 wk initially. >6 mo after 2nd trial
10	5-year-old, spayed, female Border collie	3 mo	Antibiotic flushes	90°–360°, up to 0.5 cm deep	8 wk	>11 mo

GSD = German shepherd

Ontario), 0.05 mg/kg BW, IV, and acepromazine (Atravet, Wyeth-Ayerst, Don Mills, Ontario), 0.025 mg/kg BW, IV, were used.

The age, signalment, any treatment for the anal furunculosis prior to cyclosporin therapy, and the extent of lesion involvement for each case upon presentation are shown in Table 1. Self-mutilation was reported in all dogs, except cases 5, 6, and 7; dyschezia was reported in all dogs, except cases 8 and 10. Loose or frequent bowel movements were reported in cases 1, 2, 3, and 7. Intermittent fecal incontinence was reported in case 3, after surgical treatment but prior to cyclosporin treatment. On rectal examination, firm, thickened rectal mucosa with varying degree of stricture was present in cases 1, 2, 5, 7, and 9. Anal sacs were still present in all dogs, except in cases 2, 6, and 7, which had had anal sacculectomy performed with previous surgical treatment for anal furunculosis. In addition to the cyclosporin therapy, cases 1 and 3 received trimethoprim-sulphamethoxazole and cases 4, 5, 7, 8, 9, and 10 received cephalexin. Cephalexin was discontinued after 2 and 3 d in cases 4 and 5 because of vomiting. The vomiting resolved after the cephalexin was discontinued.

There was a progressive improvement in each dog's demeanor and behavior on defecation, as well as resolution of the perianal inflammation and self-mutilation, after 1 wk of cyclosporin therapy. During the first 2 wk of cyclosporin therapy, diarrhea and dyschezia resolved in all dogs, and the frequency of bowel movements decreased in those that had previously been reported as excessive or frequent. The duration of cyclosporin therapy and the time to reduction in size of the perianal fistulas and total resolution was variable, depending on the size of the lesion, but occurred over a 2- to 20-week period (Table 1). All fistulas in all dogs resolved during cyclosporin therapy. There were no problems associated with cyclosporin therapy. No infections were seen in any of the dogs and, in fact, in those dogs not receiving antibiotics, the mucopurulent discharge associated with the fistulas resolved. The initial dosing of cyclosporin at 10 mg/kg BW, q12h, proved to exceed the 400–600 ng/mL trough target level and was reduced to

7.5 mg/kg BW, q12h. The dose was reduced further to 5 mg/kg BW, q12h, in those dogs maintaining trough levels above 600 ng/mL. Originally, antibiotic therapy was prescribed for 8 dogs; it had to be discontinued in 2 dogs because of vomiting; therefore, only 6 dogs received a course of antibiotics with cyclosporin (cases 1,3,7,8,9, and 10). In those cases in which fistulas recurred, the treatment period was only 8 wk (Table 1), although cyclosporin therapy was discontinued when the fistulas were resolved after 2 consecutive examinations, 4 wk apart. One dog required surgical excision of a fistulous tract (case 3). The fistula in question recurred repeatedly at the same site and a specific nidus was considered to be the cause. Unfortunately, the excised tissue was not submitted for histological examination. This tract was not associated with the anal sac. The presence or absence of anal sacs did not affect the final outcome in this study. The thickened rectal mucosa and functional stricture resolved in all dogs. No dog maintained or acquired fecal incontinence after cyclosporin therapy. Complete blood cell counts were not performed upon completion of cyclosporin therapy, as cyclosporin does not cause myelosuppression. At final writing of this report, all dogs, except case 2, are in remission. Remission times are recorded in Table 1.

A recent report of the pathology of surgically resected tissue from dogs with PAF identified plasma cells, lymphoid infiltrates, and neutrophils, indicated that a simple reason could not be offered for the breed predilection in GSDs (2). Similar cellular infiltrates are present in PAF associated with Crohn's disease in humans and the condition is routinely managed with standard steroid and sulfasalzine therapy (10). A group of 16 patients refractory to this standard therapy were treated with cyclosporin, which resulted in a moderate improvement in their condition (10). Dogs with PAF in this study also appeared responsive to cyclosporin treatment.

Cyclosporin is a potent immunosuppressive drug, which is used widely in organ transplantation, although its use is not restricted to this field. Due to its suppressive effects on the T-cell mediated arm of the immune system, its utility is being recognized in several immune-mediated diseases (11). Based on this action of cyclosporin and the response to its administration in the dogs in this report, we consider that an immune-mediated cause for perianal fistulas seems likely. An immunological basis has been suspected in PAF of GSDs; however, a recent study concluded that a simple immunological defect did not underlie the predisposition of GSDs to anal furunculosis (3). A clinical update on the treatment of perianal fistulas in dogs cites a study using prednisolone at 2.0 mg/kg BW, q24h, for 2 wk and 1.0 mg/kg BW, q24h, for an additional 4 wk, resulting in resolution of inflammatory bowel disease and coexisting perianal fistulas in 9 of 30 GSDs (5).

There is a constant inter- and intrapatient variability in the rate of absorption and metabolism of cyclosporin in dogs (12), which requires monitoring to ensure blood levels within therapeutic range. Based on the 100% response rate to cyclosporin, the poor response to antibiotic therapy prior to cyclosporin treatment, and the fact that 4 dogs did not receive a course of antibiotic therapy whilst receiving cyclosporin in this study, it would appear that antibiotics are not essential in managing this disease.

Because the PAF was resolved without the risk of incontinence or stricture formation, without pain or discomfort, and without the need for intensive management, all owners preferred cyclosporin over surgical treatment for their dogs. Where surgical intervention was necessary due to a persistent fistula (case 3), the preceding treatment with cyclosporin reduced the lesion to a point where only minor surgical excision was required, which, in this instance, was acceptable to the owner. In those cases in which the condition recurred, the original cyclosporin therapy was only for 8 wk. This suggests that a minimum period for cyclosporin therapy longer than 8 wk is necessary. Whether permanent remission can be attained with cyclosporin in some dogs is unknown at this time. Remission times with surgical treatment can be short, as 7 dogs in this study had surgical treatment prior to cyclosporin therapy (1 three times, 3 twice, and 3 once) (Table 1). The dogs in this report have been free of perianal fistulas for up to 19 mo.

We conclude from this study that perianal fistulas in dogs are responsive to cyclosporin therapy and the remission times at writing are superior to those obtained with surgical intervention. Surgical treatment can be reserved for those cases where cyclosporin therapy does not completely resolve the fistulas.

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References

1. Matushek KJ, Rosin E. Perianal fistulas in dogs. Compend Contin Educ Pract Vet 1991; 13: 621–630.
2. Day MJ, Weaver BMQ. Pathology of surgically resected tissue from 305 cases of anal furunculosis in the dog. J Small Anim Pract 1992; 33: 583–589.
3. Day MJ. Immunopathology of anal furunculosis in the dog. J Small Anim Pract 1993; 34: 381–388.
4. Matthieson DT, Maretta SM. Diseases of the anus and rectum. In: Slatter D, ed. Textbook of Small Animal Surgery. 2nd ed. Philadelphia: WB Saunders, 1993: 627–645.
5. Ellison GW. Clinical update: Treatment of perianal fistulas in dogs. J Am Vet Med Assoc 1995; 206: 1680–1682.
6. Elkins AD, Hobson HP. Management of perianal fistulae. A retrospective study of 23 cases. Vet Surg 1982; 11: 110–114.
7. Houlton JEF. Anal furunculosis: A review of seventy cases. J Small Anim Pract 1980; 21: 575–584.
8. MacDermott RP, Stenson WF. The role of the immune system in inflammatory bowel disease. Immunol Allergy Clin North Am 1988; 8: 521–541.
9. Killingsworth CR, Walshaw R, Reiman KA, Rosser EJ Jr. Thyroid and immunological status of dogs with perianal fistula. Am J Vet Res 1988; 49: 1742–1746.
10. Present DH, Lichtiger S. Efficacy of cyclosporine in treatment of fistula of Crohn's Disease. Dig Dis Sci 1994; 39: 374–380.
11. Bennett WM, Norman DJ. Action and toxicity of cyclosporine. Ann Rev Med 1986; 37: 215–214.
12. Mathews KA, Holmberg DL, Johnston K. Renal allograft survival in outbred mongrel dogs utilizing combination immunosuppressive drug therapy and donor bone marrow. Vet Surg 1994; 23: 347–357.